DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

FEDEX

WL No. 320-01-06

APR 19 2001

C. Krishna Prasad
Managing Director
Granules India Limited
8-3-1066 Sringar Colony
Hyderabad 500 073
India

Dear Mr. Prasad:

This is regarding an inspection of your active pharmaceutical ingredient (API) and granulation manufacturing facility in Hyderabad, India by the United States Food and Drug Administration on February 19-22, 2000. The inspection revealed significant deviations from U.S. good manufacturing practices in the manufacture of APIs and in the case of the [ ] from the CGMP regulations, and resulted in the issuance of a 26 item form FDA- 483 to you at the completion of the inspection. These deviations cause the API and granulation products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice. No distinction is made between active pharmaceutical ingredients and [ ] or finished pharmaceuticals, and failure of any to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have also reviewed your March 23, 2001 written response to the FDA-483. We acknowledge that many of the deficiencies have been corrected and the response provides a timetable for additional corrective actions. Specific areas of concern include, but are not limited to:

EQUIPMENT

1. Equipment qualification have not been completed for API manufacturing equipment currently being used and the flow of [ ] air in the [ ] production area was not properly designed to prevent or minimize cross-contamination. [FDA-483 items 12, 14]

2. Calibration of API manufacturing equipment was inadequate in that there were no written procedures or tolerance limits, there was no documentation of calibration of [ ] and an out of order [ ] was not properly identified as to its status. [FDA-483 items 6, 25]
3. Routine cleaning of API and granulation production equipment was inadequate in that there was no documentation of cleaning or changing [ ] and other equipment cleaning was not documented.[FDA-483 items 6,9,10]
4. Cleaning validation studies for multiple use [ ] equipment were inadequate in that the validation protocol did not identify the cleaning procedure, total surface area was not considered during the validation study, recovery studies were not done to validate the swab sampling method or filtering of rinse samples, some rinse samples were not analyzed, dates of analyses were inaccurate, and analytical data on rinse samples were not checked by a second person. [FDA-483 items 9, 10]

Your response includes copies of revised SOPs and training plans to correct these deficiencies, as well as protocols for new equipment qualification studies and cleaning validation to be completed within 60 days. Please keep this office advised of the status of these corrective actions and submit copies of the final study reports when they are completed.

PRODUCTION

5. Recovered solvents used in API production were not evaluated for impurities. [FDA-483 item 5]
6. Process validation for [ ] API was inadequate in that critical manufacturing and control steps were not identified, sample collection was not always documented, testing for uniformity when [ ] batches was inadequate, raw data for assay and impurity tests were missing, system suitability and resolution were not conducted on laboratory equipment when testing validation samples for impurity, and stability testing of validation batches did not evaluate impurities. [FDA-483 items 2,3,4,7]

Your response indicates that a satisfactory retrospective process validation study has been completed and that a new prospective study will be completed within 90 days. The validation protocol appears to correct the previous validation deficiencies. The response also commits to developing a solvent impurity test method and implementing appropriate testing of recovered solvents within 30 days. It also commits to conducting impurity testing on stability samples, but did not include the results for any such tests. Please keep this office informed of the status of these corrections and submit copies of the final study reports when they are completed.

LABORATORY

7. Calibration of laboratory instruments used for testing API and [ ] samples was inadequate in that written calibration procedures were missing or incomplete and the calibration of some analytical instruments was incomplete or was performed incorrectly. [FDA-483 items 8,11,18]
8. Laboratory procedures and the documentation of laboratory tests on API and [ ] samples were inadequate in that raw data was not always recorded, system suitability on laboratory equipment was sometimes not performed, the traceability of

samples was not documented, laboratory data were not verified by a second individual, [ ] testing did not use the correct reagent for the correction factor, the in-process [ ] test for one API was not validated and did not include quantification with a certified standard. [FDA-483 items 2,3,10,15,19,21]

Your response indicates these deficiencies have been corrected by the issuance of new or revised SOPs and training, and that the [ ] method validation will be completed within 15 days. Since some of these deficiencies appear to have been caused by the failure to follow existing SOPs, the effectiveness of the corrections will be further evaluated during a re-inspection of this facility.

ANNUAL REVIEWS

9. No annual reviews have been conducted on [ ] products and there was no written procedure for conducting annual reviews for [ ] products. [FDA-483 item 16]

Your response indicates that an SOP and a protocol for annual reviews have been completed, but that it will take 60 days to complete the annual reviews for the year 2000 production. Please submit a copy of the final reports to this office when they are completed.

The CGMP deviations identified above or on the FDA-483 issued to you are not to be considered as an all-inclusive list of deficiencies at this facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish to continue to ship API and [ ] products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for current good manufacturing practices.

Please respond to this letter and provide a status report on the ongoing corrective actions within 30 days, and documentation of the correction of the remaining actions when they are completed. Until FDA has reinspected this facility and confirms compliance with CGMPs and correction of these deficiencies, this office will recommend withholding approval of any new drug applications listing this facility as the manufacturer of APIs. Failure to promptly correct these deficiencies may result in the refusal to permit entry of these products into the United States.

Please direct your written response to Compliance Officer John M. Dietrick at the address shown below. Please reference CFN# 9617371 within your response.

U.S. Food & Drug Administration
CDER HFD-322
7520 Standish Place
Rockville, MD 20855-2737
Tel: (301) 594-0095
FAX (301) 594-1033

To schedule a reinspection of this facility after corrections have been completed and it is in compliance with CGMPs, contact: Director, International Drug Section, HFC-133, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, MD 20857, Tel. (301) 827-5655 or FAX (301) 443-6919.

Sincerely,

Joseph C. Famulare

Joseph C. Famulare
Director
Division of Manufacturing & Product Quality
Center for Drug Evaluation & Research

Cc:

[ ]